NDA 17-377/S-056

NOV 17 1998

Hoffman-LaRoche Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-l 199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug application dated August 8, 1997, received August 11, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bactrim™ DS (double strength) (trimethoprim and sulfamethoxazole) Tablets.

We acknowledge receipt of your submissions dated September 9, 1997 and August 27, 1998.

This supplemental new drug application provides for the addition of safety statements to the CONTRAINDICATIONS, PRECAUTIONS, and ADVERSE REACTIONS sections of the labeling, as well as numerous changes of an editorial nature.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 17-377/S-056." Approval of this submission by FDA is not required before the labeling is used.

If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

If a letter communicating important information about this drug product (i.e., a "Dear Healthcare Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Beth Duvall-Miller, Project Manager, at (301) 827-2 125.

Sincerely yours,

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

(Roche Hexagon)

APPROVED

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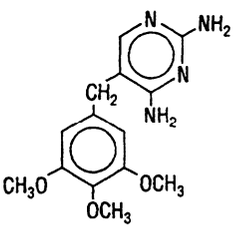
BACTRIM™
brand of
trimethoprim and
sulfamethoxazole

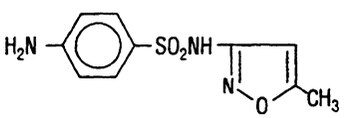
DS (double strength) TABLETS, TABLETS and PEDIATRIC SUSPENSION

DESCRIPTION: Bactrim (trimethoprim and sulfamethoxazole) is a synthetic antibacterial combination product available in DS (double strength) tablets, tablets and pediatric suspension for oral administration. Each DS tablet contains 160 mg trimethoprim and 800 mg sulfamethoxazole plus magnesium stearate, pregelatinized starch and sodium starch glycolate. Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole plus magnesium stearate, pregelatinized starch, sodium starch glycolate, FD&C Blue No. 1 lake, FD&C Yellow No. 6 lake and D&C Yellow No. 10 lake. Each teaspoonful (5 mL) of the pediatric suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole in a vehicle containing 0.3 percent alcohol, edetate disodium, glycerin, microcrystalline cellulose, parabens (methyl and propyl), polysorbate 80, saccharin sodium, simethicone, sorbitol, sucrose, FD&C Yellow No. 6, FD&C Red No. 40, flavors and water.

Trimethoprim is 2,4-diamino-5-(3,4,5 trimethoxybenzyl)pyrimidine; the molecular formula is C_{l4} H_{18} N_4 O_3 . It is a white to light yellow, odorless, bitter compound with a molecular weight of 290.3 and the following structural formula:



Sulfamethoxazole is N^1-(5-methyl-3-isoxazolyl)sulfanilamide; the molecular formula is C_{10} H_{11} N_3 O_3 S. It is almost white, odorless, tasteless compound with a molecular weight of 253.28 and the following structural formula:



CLINICAL PHARMACOLOGY: Bactrim is rapidly absorbed following oral administration. Both sulfamethoxazole and trimethoprim exist in the blood as unbound, protein-bound and metabolized forms; sulfamethoxazole also exists as the conjugated form. The metabolism of sulfamethoxazole occurs predominately by N_4-acetylation, although the glucuronide conjugate has been identified. The principal metabolites of trimethoprim are the 1- and 3-oxides and the 3'- and 4'- hydroxy derivatives. The free forms of sulfamethoxazole and trimethoprim are considered to be the therapeutically active forms. Approximately 44% of trimethoprim and 70% of sulfamethoxazole are bound to plasma proteins. The presence of 10 mg percent sulfamethoxazole

in plasma decreases the protein binding of trimethoprim by an insignificant degree; trimethoprim does not influence the protein binding of sulfamethoxazole.

Peak blood levels for the individual components occur 1 to 4 hours after oral administration. The mean serum half-lives of sulfamethoxazole and trimethoprim are 10 and 8 to 10 hours, respectively. However, patients with severely impaired renal function exhibit an increase in the half-lives of both components, requiring dosage regimen adjustment (see DOSAGE AND ADMINISTRATION section). Detectable amounts of trimethoprim and sulfamethoxazole are present in the blood 24 hours after drug administration. During administration of 160 mg trimethoprim and 800 mg sulfamethoxazole bid, the mean steady-state plasma concentration of trimethoprim was 1.72 mcg/mL. The steady-state mean plasma levels of free and total sulfamethoxazole were 57.4 mcg/mL and 68.0 mcg/mL, respectively. These steady-state levels were achieved after three days of drug administration.[1]

Excretion of sulfamethoxazole and trimethoprim is primarily by the kidneys through both glomerular filtration and tubular secretion. Urine concentrations of both sulfamethoxazole and trimethoprim are considerably higher than are the concentrations in the blood. The average percentage of the dose recovered in urine from 0 to 72 hours after a single oral dose of Bactrim is 84.5% for total sulfonamide and 66.8% for free trimethoprim. Thirty percent of the total sulfonamide is excreted as free sulfamethoxazole, with the remaining as N_4-acetylated metabolite.[2] When administered together as Bactrim, neither sulfamethoxazole nor trimethoprim affects the urinary excretion pattern of the other.

Both trimethoprim and sulfamethoxazole distribute to sputum, vaginal fluid and middle ear fluid; trimethoprim also distributes to bronchial secretion, and both pass the placental barrier and are excreted in human milk.

Microbiology: Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with *para*-aminobenzoic acid (PABA). Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Thus, Bactrim blocks two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria.

In vitro studies have shown that bacterial resistance develops more slowly with Bactrim than with either trimethoprim or sulfamethoxazole alone.

In vitro serial dilution tests have shown that the spectrum of antibacterial activity of Bactrim includes the common urinary tract pathogens with the exception of *Pseudomonas aeruginosa* The following organisms are usually susceptible: *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus mirabilis,* and indole-positive *Proteus* species including *Proteus vulgaris.* The usual spectrum of antimicrobial activity of Bactrim includes the following bacterial pathogens isolated from middle ear exudate and from bronchial secretions: *Haemophilus influenzae,* including ampicillin-resistant strains, and *Streptococcus pneumoniae. Shigella flexneri* and *Shigella sonnei* are usually susceptible. The usual spectrum also includes enterotoxigenic strains of *Escherichia coli* (ETEC) causing bacterial gastroenteritis.

BACTRIM (trimethoprim and sulfamethoxazole)

REPRESENTATIVE MINIMUM INHIBITORY CONCENTRATION **VALUES** FOR BACTRIM-SUSCEPTIBLE ORGANISMS (MIC—μg/mL)

	TMP	SMX	TMP/SMX (1:20)	
Bacteria	alone	alone	TMP	SMX
Escherichia coli	0.05-1.5	1.0-245	0.05–0.5	0.95-9.5
Escherichia coli (enterotoxigenic strains)	0.015-0.15	0.285->950	0.005-0.15	0.095-2.85
Proteus species (indole positive)	0.5-5.0	7.35-300	0.05-l .5	0.95-28.5
Morganella morganii	0.5-5.0	7.35-300	0.05-l .5	0.95-28.5
Proteus mirabilis	0.5-l.5	7.35-30	0.05-0.15	0.95-2.85
Klebsiella species	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
Enterobacter species	0.15-5.0	2.45-245	0.05-1.5	0.95-28.5
Haemophilus influenzae	0.15-l.5	2.85-95	0.015-0.15	0.285-2.85
Streptococcus pneumoniae	0.15-1.5	7.35-24.5	0.05-0.15	0.95-2.85
Shigella	<0.01-0.04	<0. 16-->320	<0.002--0.03	0.04-0.625
*Shigella sonnei**	0.02-0.08	0.625->320	0.004-0.06	0.08-l .25

TMP = trimethoprim SMX = sulfamethoxazole

*Rudoy RC, Nelson JD, Haltalin KC. *Antimicrob Agents Chemother.* May 1974;5:439-443.

The recommended quantitative disc susceptibility method may be used for estimating the susceptibility of bacteria to Bactrim.3,4 With this procedure, a report from the laboratory of "Susceptible to trimethoprim and sulfamethoxazole" indicates that the infection is likely to respond to therapy with Bactrim. If the infection is confined to the urine, a report of "Intermediate susceptibility to trimethoprim and sulfamethoxazole" also indicates that the infection is likely to respond. A report of "Resistant to trimethoprim and sulfamethoxazole" indicates that the infection is unlikely to respond to therapy with Bactrim.

INDICATIONS AND USAGE: *Urinary Tract Infections:* For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Morganella morganii, Proteus mirabilis* and *Proteus vulgaris.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Acute Otitis Media: For the treatment of acute otitis media in pediatric patients due to susceptible strains of *Streptococcuspneumoniae* or *Haemophilus influenzae* when in the judgment of the physician Bactrim offers some advantage over the use of other antimicrobial agents. To date, there are limited data on the safety of repeated use of Bactrim in pediatric patients under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

Acute Exacerbations of Chronic Bronchitis in Adults: For the treatment of acute exacerbations of chronic bronchitis due to susceptible strains of *Streptococcus pneumoniae* or *Haemophilus*

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influenzae when in the judgment of the physician Bactrim offers some advantage over the use of a single antimicrobial agent.

Shigellosis: For the treatment of enteritis caused by susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Pneumocystis Carinii Pneumonia: For the treatment of documented *Pneumocystis carinii* pneumonia and for prophylaxis against *Pneumocystis carinii* pneumonia in individuals who are imrnunosuppressed and considered to be at an increased risk of developing *Pneumocystis carinii* pneumonia.

Travelers ' Diarrhea in Adults: For the treatment of travelers' diarrhea due to susceptible strains of enterotoxigenic *E. coli.*

CONTRAINDICATIONS: Bactrim is contraindicated in patients with a known hypersensitivity to trimethoprim or sulfonamides and in patients with documented megaloblastic anemia due to folate deficiency. Bactrim is also contraindicated in pregnant patients and nursing mothers, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Bactrim is contraindicated in pediatric patients less than 2 months of age. Bactrim is also contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Complete blood counts should be done frequently in patients receiving sulfonamides.

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies have documented that patients with group A B-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than do those patients treated with penicillin, as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

PRECAUTIONS: ***General*:** Bactrim should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (eg, the elderly, chronic alcoholics,, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergies or bronchial asthma. In glucose-6-

phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Cases of hypoglycemia in non-diabetic patients treated with Bactrim are seen rarely, usually occurring after a few days of therapy. Patients with renal dysfunction, liver disease, malnutrition or those receiving high doses of Bactrim are particularly at risk.

Hematological changes indicative of folic acid deficiency may occur in elderly patients or in patients with preexisting folic acid deficiency or kidney failure. These effects are reversible by folinic acid therapy.

Trimethoprim has been noted to impair phenylalanine metabolism, but this is of no significance in phenylketonuric patients on appropriate dietary restriction.

As with all drugs containing sulfonamides, caution is advisable in patients with porphyria or thyroid dysfunction.

Use in the Elderly: There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, eg, impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS sections) or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function and duration of use should be as short as possible to minimize risks of undesired reactions (see DOSAGE AND ADMINISTRATION section). The trimethoprim component of Bactrim may cause hyperkalemia when administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or when given concomitantly with drugs known to induce hyperkalemia. Close monitoring of serum potassium is warranted in these patients. Discontinuation of Bactrim treatment is recommended to help lower potassium serum levels.

Use in the Treatment of and Prophylaxis for Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to Bactrim in the same manner as non-AIDS patients. The incidence of side effects, particularly rash, fever, leukopenia and elevated aminotransferase (transaminase) values, with Bactrim therapy in AIDS patients who are being treated for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of Bactrim in non-AIDS patients. The incidence of hyperkalemia appears to be increased in AIDS patients receiving Bactrim. Adverse effects are generally less severe in patients receiving Bactrim for prophylaxis. A history of mild intolerance to Bactrim in AIDS patients does not appear to predict intolerance of subsequent secondary prophylaxis.[5] However, if a patient develops skin rash or any sign of adverse reaction, therapy with Bactrim should be reevaluated (see WARNINGS).

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High dosage of trimethoprim, as used in patients with *Pneumocystis carinii* pneumonia, induces a progressive but reversible increase of serum potassium concentrations in a substantial number of patients. Even treatment with recommended doses may cause hyperkalemia when trimethoprim is administered to patients with underlying disorders of potassium metabolism, with renal insufficiency, or if drugs known to induce hyperkalemia are given concomitantly. Close monitoring of serum potassium is warranted in these patients.

During treatment, adequate fluid intake and urinary output should be ensured to prevent crystalluria. Patients who are "slow acetylators" may be more prone to idiosyncratic reactions to sulfonamides.

Information for Patients: Patients should be instructed to maintain an adequate fluid intake in order to prevent crystalluria and stone formation.

Laboratory Tests: Complete blood counts should be done frequently in patients receiving Bactrim; if a significant reduction in the count of any formed blood element is noted, Bactrim should be discontinued. Urinalyses with careful microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Bactrim is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Bactrim may inhibit the hepatic metabolism of phenytoin. Bactrim, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites and can compete with the renal transport of methotrexate, thus increasing free methotrexate concentrations.

There have been reports of marked but reversible nephrotoxicity with coadministration of Bactrim and cyclosporine in renal transplant recipients.

Increased digoxin blood levels can occur with concomitant Bactrim therapy, especially in elderly patients. Serum digoxin levels should be monitored.

Increased sulfamethoxazole blood levels may occur in patients who are also receiving indomethacin.

Occasional reports suggest that patients receiving pyrimetharnine as malaria prophylaxis in doses exceeding 25 mg weekly may develop megaloblastic anemia if Bactrim is prescribed.

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The efficacy of tricyclic antidepressants can decrease when coadministered with Bactrim.

Like other sulfonamide-containing drugs, Bactrim potentiates the effect of oral hypoglycemics.

In the literature, a single case of toxic delirium has been reported after concomitant intake of trimethoprim/sulfamethoxazole and amantadine.

Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffe alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis:* Long-term studies in animals to evaluate carcinogenic potential have not been conducted with Bactrim.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage was observed in human leukocytes cultured in vitro with sulfamethoxazole and trimethoprim alone or in combination; the concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole. These doses are 10.9-fold higher than the recommended human dose for trimethoprim and sulfamethoxazole.

Pregnancy: Teratogenic Effects: Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole (16.7.fold higher than the recommended human dose) or 200 mg/kg trimethoprim (31.3-fold higher than the recommended human dose) produced teratologic effects manifested mainly as cleft palates.

The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole (16-fold higher than the recommended human dose) or 192 mg/kg trimethoprim (30-fold higher than the recommended human dose) when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole (16-fold higher than the recommended human dose) was used in combination with 128 mg/kg of trimethoprim 20-fold higher than the recommended human dose). In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole (11.l-fold higher than the recommended human dose), was used in combination with 88 mg/kg of trimethoprim (13.8 -fold higher than the recommended human dose).

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In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

While there are no large, well-controlled studies on the use of trimethoprim and sulfamethoxazole in pregnant women, Brumfitt and Pursell,[6] in a retrospective study, reported the outcome of 186 pregnancies during which the mother received either placebo or trimethoprim and sulfamethoxazole. The incidence of congenital abnormalities was 4.5% (3 of 66) in those who received placebo and 3.3% (4 of 120) in those receiving trimethoprim and sulfamethoxazole. There were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.

Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, Bactrim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: See CONTRAINDICATIONS section.

Nursing Mothers: See CONTRAINDICATIONS section.

Pediatric Use: Bactrim is not recommended for pediatric patients younger than 2 months of age (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria).
FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia, pancytopenia, purpura.

Allergic Reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. In addition, periarteritis nodosa and systemic lupus erythematosus have been reported.

Gastrointestinal: Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia.

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Genitourinary: Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria and nephrotoxicity in association with cyclosporine.

Metabolic and Nutritional: Hyperkalemia (see PRECAUTIONS: Use *in the Elderly and Use in the Treatment of and Prophylaxis for Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome [AIDS]).*

Neurologic: Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache.

Psychiatric: Hallucinations, depression, apathy, nervousness.

Endocrine: The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents. Cross-sensitivity may exist with these agents. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides.

Musculoskeletal: Arthralgia and myalgia. Isolated cases of rhabdomyolysis have been reported with Bactrim, mainly in AIDS patients.

Respiratory: Pulmonary infiltrates.

Miscellaneous: Weakness, fatigue, insomnia.

OVERDOSAGE: *Acute:* The amount of a single dose of Bactrim that is either associated with symptoms of overdosage or is likely to be life-threatening has not been reported. Signs and symptoms of overdosage reported with sulfonamides include anorexia, colic, nausea, vomiting, dizziness, headache, drowsiness and unconsciousness. Pyrexia, hematuria and crystalluria may be noted. Blood dyscrasias and jaundice are potential late manifestations of overdosage.

Signs of acute overdosage with trimethoprim include nausea, vomiting, dizziness, headache, mental depression, confusion and bone marrow depression.

General principles of treatment include the institution of gastric lavage or emesis, forcing oral fluids, and the administration of intravenous fluids if urine output is low and renal function is normal. Acidification of the urine will increase renal elimination of trimethoprim. The patient should be monitored with blood counts and appropriate blood chemistries, including electrolytes. If a significant blood dyscrasia or jaundice occurs, specific therapy should be instituted for these complications. Peritoneal dialysis is not effective and hemodialysis is only moderately effective in eliminating trimethoprim and sulfamethoxazole.

Chronic: Use of Bactrim at high doses and/or for extended periods of time may cause bone marrow depression manifested as thrombocytopenia, leukopenia and/or megaloblastic anemia. If signs of bone marrow depression occur, the patient should be given leucovorin 5 to 15 mg daily until normal hematopoiesis is restored.

BACTRIM (trimethoprim and sulfamethoxazole)

DOSAGE AND ADMINISTRATION: Not recommended for use in pediatric patients less than 2 months of age.

Urinary Tract Infections and Shigellosis in Adults and Pediatric Patients, and Acute Otitis Media in Pediatric Patients:

Adults: The usual adult dosage in the treatment of urinary tract infections is 1 Bactrim DS (double strength) tablet, 2 Bactrim tablets or 4 teaspoonfuls (20 mL) of Bactrim Pediatric Suspension every 12 hours for 10 to 14 days. An identical daily dosage is used for 5 days in the treatment of shigellosis.

Pediatric Patients: The recommended dose for pediatric patients with urinary tract infections or acute otitis media is 8 mg/kg trimethoprimand 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses every 12 hours for 10 days. An identical daily dosage is used for 5 days in the treatment of shigellosis. The following table is a guideline for the attainment of this dosage:

Pediatric Patients 2 months of age or older:

Weight		Dose – every 12 hours	
lb	Kg	Teaspoonfuls	Tablets
22	10	1(5mL)	–
44	20	2 (10 mL)	1
66	30	3 (15 mL)	1 1/2
88	40	4 (20 mL)	2 or 1 DS tablet

For Patients with Impaired Renal Function: When renal function is impaired, a reduced dosage should be employed using the following table:

Creatinine Clearance (mL/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	1/2 the usual regimen
Below 15	Use not recommended

Acute Exacerbations of Chronic Bronchitis in Adults:

The usual adult dosage in the treatment of acute exacerbations of chronic bronchitis is 1 Bactrim DS (double strength) tablet, 2 Bactrim tablets or 4 teaspoonfuls (20 mL) of Bactrim Pediatric Suspension every 12 hours for 14 days.

Pneumocystis Carinii Pneumonia:

Treatment: Adults and Pediatric Patients:

The recommended dosage for treatment of patients with documented *Pneumocystis carinii* pneumonia is 15 to 20 mg/kg trimethoprim and 75 to 100 mg/kg sulfamethoxazole per 24 hours given in equally divided doses every 6 hours for 14 to 2 1 days. The following table is a guideline for the upper limit of this dosage.

BACTRIM (trimethoprim and sulfamethoxazole)

Weight		Dose-every 6 hours	
lb	kg	Teaspoonsful	Tablets
18	8	1 (5 mL)	–
35	16	2 (10 mL)	1
53	24	3 (15 mL)	1 1/2
70	32	4 (20 mL)	2 or 1 DS tablet
88	40	5 (25 mL)	2 1/2
106	48	6 (30 mL)	3 or 1 1/2 DS tablets
141	64	8 (40 mL)	4 or 2 DS tablets
176	80	10 (50 mL)	5 or 2 1/2 DS tablets

For the lower limit dose (15 mg/kg trimethoprim and 75 mg/kg sulfamethoxazole per 24 hours) administer 75% of the dose in the above table.

Prophylaxis:

Adults:

The recommended dosage for prophylaxis in adults is 1 Bactrim DS (double strength) tablet daily. *

Pediatric Patients:

For pediatric patients, the recommended dose is 150 mg/m2/day trimethoprim with 750 mg/m*/day sulfamethoxazole given orally in equally divided doses twice a day, on 3 consecutive days per week. The total daily dose should not exceed 320 mg trimethoprim and 1600 mg sulfamethoxazole. The following table is a guideline for the attainment of this dosage in pediatric patients:

Body Surface Area	Dose-every 12 hours	
(m^2)	Teaspoonfuls	Tablets
0.26	1/2 (2.5 mL)	–
0.53	1 (5 mL)	1/2
1.06	2 (10 mL)	1

Travelers' Diarrhea in Adults:

For the treatment of travelers' diarrhea, the usual adult dosage is 1 Bactrim DS (double strength) tablet; 2 Bactrim tablets or 4 teaspoonfuls (20 mL) of Pediatric Suspension every 12 hours for 5 days.

HOW SUPPLIED: *DS (double strength) Tablets* (white, notched, capsule shaped), containing 160 mg trimethoprim and 800 mg sulfamethoxazole-bottles of 100 (NDC 0004-0117-01), 250 (NDC 0004-0117-04) and 500 (NDC 0004-0117-14). Imprint on tablets: (front) BACTRIM-DS; (back) ROCHE.

Tablets (light green, scored, capsule shaped), containing 80 mg trimethoprim and 400 mg sulfamethoxazole-bottles of 100 (NDC 0004-0050~01). Imprint on tablets: (front) BACTRIM; (back) ROCHE.

BACTRIM (trimethoprim and sulfamethoxazole)

Pediatric Suspension (pink, cherry flavored), containing 40 mg trimethoprirn and 200 mg sulfamethoxazole per teaspoonful (5 mL)-bottles of 16 oz (1 pint) (NDC 0004-l 033-28).

TABLETS SHOULD BE STORED AT 15° to 30°C (59" to 86°F) IN A DRY PLACE AND PROTECTED FROM LIGHT.

SUSPENSION SHOULD BE STORED AT 15° to 30°C (59" to 86°F) AND PROTECTED FROM LIGHT.

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(Roche Hexagon)

Pharmaceuticals

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